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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,631	07/21/2003	Luigi Grasso	MOR-0241/HD0002 US	9935

23377 7590 03/28/2006

WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE, 46TH FLOOR
1650 MARKET STREET
PHILADELPHIA, PA 19103

EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,631	GRASSO ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-65 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-65 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Examiner Notes

Claims 33-35 are improperly dependent. Amendment to claim language is suggested.

Claim 16 is an improperly dependent claim, and therefore Claim 1 does not link Invention I and Invention II. Should Applicant correlate the method of identifying genes responsible for high titer antibody production with the method of making a transgenic animal, Applicant should provide such documentation and amend the claims to reflect such a correlation. Otherwise, the claims will be treated as independent and distinct inventions, as reflected in the restriction requirements below.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-15, 17-18 and 65-66, drawn to a method for identifying genes responsible for high titer antibody production, classified in class 435, subclass 6.

II. Claim 16, drawn to a method of making a transgenic animal derived from a high titer antibody producing, inactivated mismatch repair fertilized egg cell, classified in class 800, subclass 21.

III. Claims 19-35 and 42-49, drawn to methods for modulating antibody production of cells, classified in class 435, subclass 55.

IV. Claims 36-41, drawn to methods for selecting cells for high titer antibody production, classified in class 435, subclass 6.

V. Claims 50-64, drawn to a host cell for the expression of antibody molecules comprising a defect in the expression of the monocyte-activating polypeptide I and/or the alpha-1-antitrypsin genes, classified in class 435, subclass 69.6.

Inventions I-V are patentably distinct because,

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, Invention I is drawn to a method for identifying genes responsible for high titer antibody production; whereas, Invention II is drawn to a method of making a transgenic animal derived from a high titer antibody producing fertilized egg cell. By definition, a transgenic animal contains an exogenously-derived gene. However, Invention I recites alternative genetic sources for the immunoglobulin genes, wherein the gene may only be of endogenous derivation. A transgenic animal is not required to identify high titer antibody producing genes. The method to identify genes is of distinctly different objective, design and materially different effect than, and mutually exclusive from, the method to create a transgenic animal. The Invention II process of making a transgenic animal from a high-titer antibody-producing cell can also be achieved by nuclear transplant, wherein the nucleus of a non-embryonic stem cell, phenotypically demonstrating high-titer antibody production, is introduced into an enucleated egg cell. Furthermore, the high-titer antibody producing fertilized egg cells recited in Invention I need not be used to create a transgenic animal. Instead, they may be immortalized *in vitro* to generate a high-yielding antibody cell line.

Because these inventions are materially and structurally distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Inventions III-V are unrelated. In the instant case, Invention III is drawn to methods for modulating antibody production of cells. Invention IV is drawn to methods for selecting cells for high titer antibody production. Invention V is drawn to a host cell for the expression of antibody molecule comprising a defect in the expression of the alpha-1-antitrypsin and/or monocyte-activating polypeptide I gene products. The Invention III methods to modulate antibody production in cells do not require the Invention V disclosed expression vector. Thus, the Invention V modes of operation and effects are distinctly different, mutually exclusive of, and not disclosed as capable of use together with the Invention III methods. The Invention IV method

steps are distinctly different in design, mode of operation and effect than the Invention III methods to produce cells appropriately treated to affect expression of the alpha-1-antitrypsin and monocyte-activating polypeptide I gene products, and the Invention V method steps to inactivate or decrease expression of the alpha-1-antitrypsin and monocyte-activating polypeptide I gene products. The Invention IV methods to select cells are based upon assays that measure the RNA and protein levels of alpha-1-antitrypsin and monocyte-activating polypeptide I. These assay steps do not require the host cells to have any designed genetic alteration as disclosed for Inventions III and V.

Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Inventions I-II and Inventions III-V are unrelated. In the instant case, the Invention I method to identify genes involved in high titer antibody production is mutually exclusive of, is not disclosed as capable of use together with, and of distinctly different objective, design, and effect than Inventions III -V. The Invention I method is designed to inactivate the mismatch repair genes in the host cell, and then screen for changes in total RNA and protein expression levels. These Invention I genetic alteration methods are directed towards distinctly different genes than the alpha-1-antitrypsin and monocyte-activating polypeptide I genes recited for Inventions III-V, and therefore are of distinctly different designs and effects. The mismatch repair genes encode distinctly different proteins that perform distinctly different functions than alpha-1-antitrypsin and monocyte-activating polypeptide I genes and their respective gene products. Additional Invention I screening assays include analysis for changes in particular genomic nucleotides and analysis of the cellular phenotypes in response to genetic alterations in an identified gene. In contrast, the Invention IV methods to select cells for high titer antibody production focus their analyses on changes in the RNA and protein expression levels of alpha-1-antitrypsin and monocyte-activating polypeptide I genes. Furthermore, the Invention II method of creating a transgenic animal is of materially different objective, design and effect than, and not disclosed as capable of use together with the Invention III methods to modulate antibody

production, the Invention IV methods to select cells based upon assays that measure the RNA and protein levels of alpha-1-antitrypsin and monocyte-activating polypeptide I, and the Invention V host cells for the expression of antibody molecules. The cells of Inventions III and V are developmentally incapable on their own to produce a transgenic animal, and the disclosed genetic alterations of the Invention II cells to inactivate mismatch repair are materially distinct than the disclosed genetic alterations of the Inventions III-V cells. Furthermore, the Invention I cells are disclosed to neither contain nor require the expression vector comprising the light and heavy immunoglobulin genes as recited for the Invention V cells.

Because these inventions are materially and structurally distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Should Applicant elect either Inventions I, III or V, further group restriction to one of the following under 35 USC 121. Therefore, election is required of Invention I, III or V and one of inventive groups (a)-(l) below, regarding a patently distinct molecular mutation or composition to inactivate the expression of the target gene product (see Claims 6-10 and 26-31, for example), specifically:

a) a dominant-negative allele directed against the target gene,

b) a truncation mutation directed against the target gene,

c) an RNA interference molecule directed against the target gene,

d) an antisense oligonucleotide directed against the target gene,

e) an expression vector containing an antisense transcript directed against the target gene,

f) a knock-out mutation to disrupt the endogenous function of the target gene,

g) a polynucleotide containing a ribozyme directed against the target gene,

h) a neutralizing antibody against the target gene product,

i) an intracellular blocking antibody against the target gene product,

j) a compound that decreases the activity of target gene product,

k) a compound that decreases the level of the target gene product, or

l) a frameshift mutation to disrupt the endogenous function of the target gene.

Claims 1 and 17 link Inventions I, III and V, inventive groups (a)-(f).
Claims 19, 44 and 47 link Inventions I, III and V, inventive groups (d)-(i) and (k).
Claims 50 and 56 link Inventions I, III and V, inventive groups (e)-(h) and (j).

Inventions I, III and V, inventive groups (a)-(l) are distinct because,

Inventions I, III and V, inventive groups (a)-(l) are unrelated. Antisense oligonucleotides, antisense transcripts, ribozymes, and knock-out, frameshift, and truncation targeting vectors are polynucleotides; whereas neutralizing and blocking antibodies are polypeptides. Applicants are reminded that nucleic acid sequences and amino acid sequences are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleic acid and amino acid sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Furthermore, inactivating mutations may have two modes of operation, *cis-* or *trans-*. *Cis*-acting mutations molecularly exist within a first, target nucleic acid molecule and directly affect all products encoded by that first, target nucleic acid molecule. *Trans*-acting mutations molecularly exist in a second nucleic acid molecule, but whose effect is achieved by the product of the second nucleic acid molecule acting on the product of a first, target nucleic acid molecule. The knock-out mutation is a *cis*-acting allele and will structurally alter the genome of the antibody producing cell, and thus has a materially different design and mode of action, than the other mutations and compositions. The dominant-negative alleles, truncation mutations, RNA interference molecules and antisense molecules are all *trans*-acting mutations. Additionally, the *trans*-acting mutations may exist external to the nuclear chromosomes, encoded as episomal vectors, and thus are physically separable from an isolated nucleus. However, the knock-out mutation directly alters the nuclear genome and will not be separable from an isolated nucleus. Thus, the active compositions responsible for decreasing expression of the target gene are structurally distinct, are not obvious variants, have different

modes of operation and effect, are mutually exclusive, and are not disclosed as capable of use together with the other compositions.

Because these inventions are inherently distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed method step to inactivate the expression of the target gene product for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Failure to elect a method step consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

For Invention I above, a group restriction to one of the following is also required under 35 USC 121. Therefore, election is required of Invention I and a method step to inactivate or reduce expression of a mismatch repair gene from inventive groups (a)-(l) above and one of inventive groups (m)-(o) below, regarding expression of a patently distinct immunoglobulin gene (see Claims 2-5, for example), specifically:

m) endogenous immunoglobulin genes,

n) exogenous immunoglobulin genes, or

o) derivatives of immunoglobulin genes.

Claim 1 links Invention I, inventive groups (m)-(o).

Invention I, inventive groups (m)-(o) are distinct because,

Invention I, inventive groups (m)-(o) are unrelated. The endogenous immunoglobulin gene is structurally distinct from an immunoglobulin gene, or fragment thereof, introduced from an external source. The endogenous immunoglobulin gene contains introns the must be removed prior to translation to create an intact immunoglobulin molecule; whereas, an exogenously derived immunoglobulin gene does not necessarily contain introns. Furthermore, the endogenous immunoglobulin gene will be of an un-designed sequence, produced by random chance; whereas,

the coding region of the exogenous immunoglobulin gene will be of specific design. Furthermore, the exogenously-derived immunoglobulin genes exist external to the nuclear chromosomes, encoded as episomal vectors, and thus are physically separable from an isolated nucleus. However, the endogenous immunoglobulin gene exists within the nuclear genome and will not be separable from an isolated nucleus. Applicants are reminded that nucleic acid sequences encoding different proteins, and the amino acid sequences they encode, are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleic acid and amino acid sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Thus, the immunoglobulin genes, and fragments thereof, are not obvious variants of each other, are mutually exclusive and can have materially different design, function and effect.

Because these inventions are materially and structurally distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed source and composition of the immunoglobulin gene expressed by the antibody-producing cell for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Failure to elect an immunoglobulin gene consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Should Applicant elect Invention I and a method step to inactivate or reduce expression of a mismatch repair gene from inventive groups (a)-(l) and one of Invention I, inventive groups (m)-(o) from above reciting a source of immunoglobulin genes, further group restriction is required.

For invention Inventions I above, restriction to one of the following is also required under 35 USC 121. Therefore, election is required of Invention I and a method step to inactivate or reduce expression of a mismatch repair gene from inventive groups (a)-(l) and one of Invention I,

inventive groups (m)-(o) from above reciting a source of immunoglobulin genes and one of inventive groups (p)-(s) below, regarding a patently distinct molecular screening assay (see Claims 11-14, for example), specifically:

p) analyzing a nucleotide sequence of the genome,

q) analyzing mRNA expression levels and structure,

r) analyzing protein, or

s) analyzing the phenotype.

Claim 1 links Invention I, inventive groups (p)-(s).

Invention I, inventive groups (p)-(s) are distinct because,

Invention I, inventive groups (p)-(s) are unrelated. Phenotypic analysis is generic to a universe of possibilities, and is directly dependent upon the chosen means of measurement. The method steps to molecularly assay a nucleotide sequence of the genome are distinctly different in design and mode of operation than the steps to molecularly assay mRNA expression levels, mRNA structures or proteins. Each assay provides a distinct set of information that may correlate with, but is neither identical nor equivalent to, the information set yielded from another assay. The molecular screening assays are not obvious variants of each other, are mutually exclusive and have materially different design, function and effect.

Because these inventions are inherently distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed step of screening cells for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Failure to elect a molecular screening assay consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Should Applicant elect Invention I and a method step to inactivate or reduce expression of a mismatch repair gene from inventive groups (a)-(l) and one of Invention I, inventive groups

(m)-(o) reciting a source of immunoglobulin genes and a distinct method step to screen cells (p)-(s) from above, a species restriction is required.

Claims 1 and 17 are generic to a plurality of disclosed patentably distinct species comprising a high titer antibody producing cell that is mismatch repair defective. Furthermore, Claims 15 and 18 contain an improper Markush Groups that is not compliant with *In re Harnisch* and recites different mismatch repair defective, antibody producing cells. Thus, form paragraph *M.P.E.P. 8.01 Election of Species* does not apply. Each cell type is genetically, chemically and biologically distinct from the others. The cells express distinctly different arrays of protein, thus creating distinctly different cellular, biochemical and metabolic environments and effects. Furthermore, bacterial, yeast, plant and animal cells have distinctly different developmental potentials. The cell types are not obvious variants of each other, are mutually exclusive and have materially different design, function and effect.

Because these inventions are inherently distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

For Invention I above, restriction to one of the following species is also required under 35 USC 121. Therefore, election is required of Invention I and a method step to inactivate or reduce expression of a mismatch repair gene from inventive groups (a)-(l) and one of Invention I, inventive groups (m)-(o) reciting a source of immunoglobulin genes and a distinct method step to screen cells from Invention I, inventive groups (p)-(s) from above and one of invention species (i)-(x) below, regarding a patently distinct mismatch repair defective, antibody producing cells, specifically:

i) a fertilized egg of a non-human animal,

ii) a bacterial cell,

iii) a yeast cell,

iv) a plant cell,

v) a mammalian cell,

vi) a mouse cell,

vii) a rat cell,

vii) a rabbit cell,

ix) a hamster cell, or

x) a non-human primate cell.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed specie of a high titer antibody producing cell that is mismatch repair defective for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Failure to a specie consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Should Applicant elect Invention III and a method step from inventive groups (a)-(l) above to inactivate or reduce expression of the target gene product, further Group restriction is required under 35 U.S.C. 121.

A. Claim 34, drawn to a method for enhancing antibody production of cells comprising steps to contact said cells with a blocking antibody to natural protease inhibitors, classified in class 435, subclass 55.

B. Claims 35 and 44-46, drawn to a method for enhancing antibody production of cells comprising steps to inactivate or impair expression of the monocyte-activating polypeptide I gene product, classified in class 435, subclass 55.

C. Claims 47-49, drawn to a method for enhancing antibody production of cells comprising steps to inactivate or impair expression of the monocyte-activating polypeptide I gene product, classified in class 435, subclass 55.

D. Claims 32-33, drawn to a method for suppressing antibody production of cells comprising contacting said cells with pharmacological amounts of protease inhibitors, classified in class 435, subclass 55.

E. Claim 42, drawn to a method for suppressing antibody production of cells comprising contacting said cells with at least compound that increases monocyte-activating polypeptide I expression, classified in class 435, subclass 55.

F. Claim 43, drawn to a method for suppressing antibody production of cells comprising contacting said cells with at least compound that increases alpha-1-antitrypsin expression, classified in class 435, subclass 55.

Claims 19-31 link Invention III, Groups A-C.

Invention III, Groups A-F are distinct because,

Invention III, Groups A-F are unrelated. The Groups A-C methods to enhance antibody production are of distinctly different objectives, designs and effects than, and are not disclosed as capable of use together with, the Groups D-F methods to suppress antibody production. Furthermore, The Group A blocking antibody and the Groups B and C active compositions responsible for decreasing expression of the alpha-1-antitrypsin and monocyte-activating polypeptide I target genes are structurally distinct, are not obvious variants, have different modes of operation and effect, are mutually exclusive, and are not disclosed as capable of use together with the other compositions. The alpha-1-antitrypsin and monocyte-activating polypeptide I genes are distinctly different nucleic acid sequences and encode molecules with distinctly different effects. The compounds to increase the expression of the alpha-1-antitrypsin and monocyte-activating polypeptide I genes are disclosed to be mutually exclusive, not capable of use together with and having different effects than the protease inhibitors. Both the protease inhibitors and compounds are recited generically and are of undisclosed identity, and thus encompass a universe of molecular structures, including nucleic acid polymers and amino acid polymers. Applicants are reminded that nucleic acid sequences and amino acid sequences are structurally distinct chemical compounds and are unrelated to one another.

Because these inventions are inherently distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome

for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Should Applicant elect Invention III and one of inventive groups (a)-(l) method steps to inactivate or reduce expression of the target gene product and either Invention III, Group B or C above, a species restriction is required.

This application contains claims directed to the following patentably distinct species of high titer antibody producing cells (i)-(vi) below. Currently, Claims 19 is generic. Election is required of Invention III and one of inventive groups (a)-(l) method steps to inactivate or reduce expression of the target gene product and either Invention III, Group B or C above and a patently distinct specie of high titer antibody producing cells, specifically:

i) hybridoma,

ii) epithelial,

iii) ovarian,

iv) kidney,

v) myeloid, or

vi) lymphoid.

The species are independent or distinct because each cell type is of a distinct developmental origin and expresses a distinctly different panel of genes and gene products resulting in unique cellular and metabolic environments. These unique cellular environments may impose distinctly different effects on the efficiency by which immunoglobulin gene products are produced. Furthermore, hybridoma cells are known in the art to be the result of cell fusion between an antibody-producing cell and a tumor lymphocyte. The hybridoma cell is both genetically transformed and immortalized; whereas, the other cells may be of primary origin and not yet immortalized. Thus, the developmental potential of each cell type is biologically restricted and mutually exclusive.

Because these inventions are inherently distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome

for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed specie of a high titer antibody producing cells for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Failure to a specie consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Should Applicant elect Invention IV from above, further Group restriction is required.

A. Claims 36-38, drawn to a method for selecting cells for high titer antibody production whereby growth medium of cells is analyzed for alpha-1-antitrypsin, classified in class 435, subclass 6.

B. Claims 39-41, drawn to a method for selecting cells for high titer antibody production whereby growth medium of cells is analyzed for monocyte-activating polypeptide I, classified in class 435, subclass 6.

The Invention IV, Groups A and B are distinct because,

Invention IV, Groups A and B are unrelated. The Invention IV, Groups A and B methods to select cells are based upon assays that measure the RNA and protein levels of alpha-1-antitrypsin and monocyte-activating polypeptide I, respectively. The Group A molecular reagents to assay alpha-1-antitrypsin gene products are mutually exclusive and structurally distinct than the Group B molecular reagents to assay monocyte-activating polypeptide I gene products.

Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect either Invention IV, Group A or B for prosecution on the merits to which the claims shall be restricted if no generic claim is finally

held to be allowable. Failure to elect an Invention IV Group consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Should Applicant elect Invention V and a method step of inventive groups (a)-(l) above to inactivate or reduce expression of the target gene product, further Group restriction is required under 35 U.S.C. 121.

A. Claims 50-55, drawn to a host cell for the expression of antibody molecules comprising a defect in the expression of the monocyte-activating polypeptide I gene, classified in class 435, subclass 69.6.

B. Claims 56-64, drawn to a host cell for the expression of antibody molecules comprising a defect in the expression of the alpha-1-antitrypsin gene, classified in class 435, subclass 69.6.

The Invention V, Groups A and B are distinct because,

Invention V, Groups A and B are unrelated. The modes of operation and effects of Invention V, Groups A and B are distinctly different, mutually exclusive of, and not disclosed as capable of use together. The Group A molecular reagents to affect the monocyte-activating polypeptide gene products are materially distinct than the Group B molecular reagents affecting alpha-1-antitrypsin gene products. The monocyte-activating polypeptide I gene encodes a distinctly different protein that performs a distinctly different function than alpha-1-antitrypsin gene product. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect either Invention V, Group A or B for prosecution on the merits to which the claims shall be restricted if no generic claim is finally

held to be allowable. Failure to elect an Invention V Group consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Should Applicant elect Invention V, Group B and a single disclosed method step of inventive groups (a)-(l) above to inactivate or reduce expression of the target gene product, further group restriction is required under 35 U.S.C. 121.

Therefore, election is required of Invention V, Group B and a single disclosed method step of inventive groups (a)-(l) to inactivate or reduce expression of the target gene product from above and one of inventive groups (m)-(p) below, regarding patently distinct immunoglobulin genes (see Claims 62-64, for example), specifically:

m) a light chain immunoglobulin gene,

n) a fragment of the light chain immunoglobulin gene,

o) a heavy chain immunoglobulin gene, or

p) a fragment of the heavy chain immunoglobulin gene.

Claim 56 links Invention V, Group B, inventive groups (m)-(p).

Invention V, Group B, inventive groups (m)-(p) are distinct because,

Invention V, Group B, inventive groups (m)-(p) are unrelated. The exogenously-derived immunoglobulin genes, and fragments thereof, are not obvious variants of each other, are mutually exclusive and can have materially different design, function and effect. The exogenously-derived immunoglobulin light gene and immunoglobulin heavy gene are distinctly different nucleic acid sequences and encode molecules with distinctly different function. Similarly, the genes encoding full-length and fragmentary immunoglobulin proteins are distinctly different nucleic acid sequences and encode molecules with distinctly different effects. Applicants are reminded that nucleic acid sequences encoding different proteins, and the amino acid sequences they encode, are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleic acid and amino acid sequence is presumed to represent an independent and distinct

invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq.

Because these inventions are inherently distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed immunoglobulin gene for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Failure to elect an immunoglobulin gene inventive group consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER

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